Remarks

This Reply is responsive to the Final Office Action dated December 3, 2004 and is filed with a petition for a one-month extension of time and authorization to charge the extension fee (small entity) to deposit account No 50-0951. This Reply is accompanied by a Rule 132 declaration (hereafter the "Declaration") marked as Exhibit "A" which provides sworn testimony from Inventor Dr. Talton.

Claims 28-44 and 48-70 were pending at the time of the Office Action. All claims were rejected. No claims have been amended herein. Method claims 68-70 have been cancelled, without prejudice. No new matter has been added.

Claims 28, 30-45, 48, 50-54, and 59-61 (drawn to coated medicament) were rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,223,244 to Moro et al. ("'244"), in view of U.S. Patent No. 5,976,577 to Green et al. ("'Green"). Claims 28, 30-45, 48-61, and 66-67 were rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,972,388 to Sakon et al., ("'Sakon) in view of Green. Claims 28, 30-45, 48, 59-61, and 66-67 were rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,855,913 to Hanes et al., ("Hanes") in view of Green. Claims 62-65 were rejected under 35 U.S.C. §103(a) as being unpatentable over Moro or Sakon or Hanes in view of U.S. Patent No. 6,277,364 to Bucks et al., ("Bucks"). Claims 29 and 68-70 were rejected under U.S.C. §103(a) as being unpatentable over Moro or Sakon or Hanes in view of Lowndes and further in view of Green. No basis for rejection of claim 29 was articulated in the Final Office Action. Claim 29 recites a coating layer which "is exclusive of said drug provided by said drug particles".

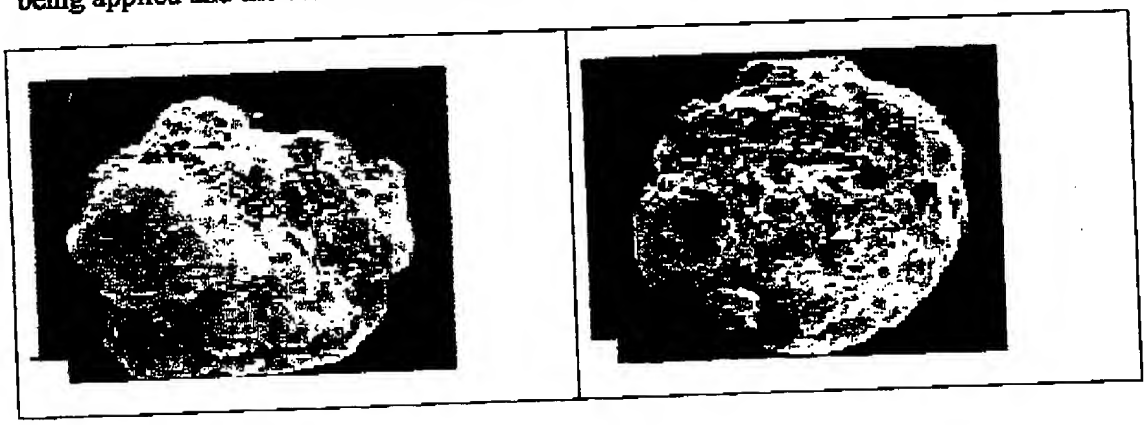
Before reviewing the cited art, Applicants will first review the claimed invention as recited in claim 28. Claim 28 recites a medicament comprising a plurality of coated drug particles, each coated drug particle having an average particle size of less than 50 μm in diameter, the surface of the particles comprising at least a first coating layer. The coating layer is a continuous and non-porous layer. The coating particles are biodegradable or biocompatible. The biodegradable or biocompatible coating layer provides controlled drug delivery. The average thickness of the coating layer is from 1 to 500 nm. The enabling technology described in the present application is a process comprising pulsed laser ablation. Laser ablation is an inherently dry process.

Such thinly coated medicaments are not possible using other known methods for coating core drug particles (see Applicants' background; page 1, lines 23-30). Core drug particles having very thin (including nanoscale) continuous and non-porous coatings are evidenced by sustained release profiles are provided throughout Applicants' specification as well as by Example 1, page 33, lines 18-20. Porous coatings, such as inherently resulting from *solvent evaporation in spray processing when used to form nanoscale coatings* as claimed by Applicants, clearly cannot provide sustained release profiles. Applicants have previously provided a paper (Maa et al, 1996, Intl. J. Pharmaceutics 144:47-59) and cited U.S. Pat. No. 5,437,889 to Jones which clearly demonstrate that when spray processing is used, because the typical droplet size generated is 10-20 microns, the core particles must be at least about 75 to 100 μm or larger to obtain continuous coatings. Paragraph 5 of the Declaration testifies to this fact.

As testified to in paragraph 10 of the Declaration, the porous coated particles produced by spray coating methods become non-discrete, as they are agglomerated in a porous continuous phase:

In Moro, Sakon and Hanes, the solvent and other volatile species rapidly evaporate to leave a random mixture of the remaining non-volatile species intermixed, with the resulting layer formed having significant porosity from the solvent evaporation process. No distinguishable coating layer is formed on any species since the arrangement of particles following drying is random, being a porous continuous phase having a plurality of core particles therein. As a result, spray drying does not form a plurality of coated particles, and clearly cannot provide a medicament comprising < 50 micron core drug particles coated with a nanoscale continuous and non-porous coating layer.

SEM images of a porous continuous phase having a plurality of core particles therein is shown below, the black spots being pores, which result from liquid coatings being applied and then the solvent evaporating off quickly:



As in the previous Office Action dated March 30, 2004, Green is again used by the Examiner in an attempt to make up for the admitted deficiencies of Moro, Sakon, and Haynes which according to the Examiner "do not explicitly teach that the coating layer is a continuous and non-porous layer".

According to the Examiner regarding Green:

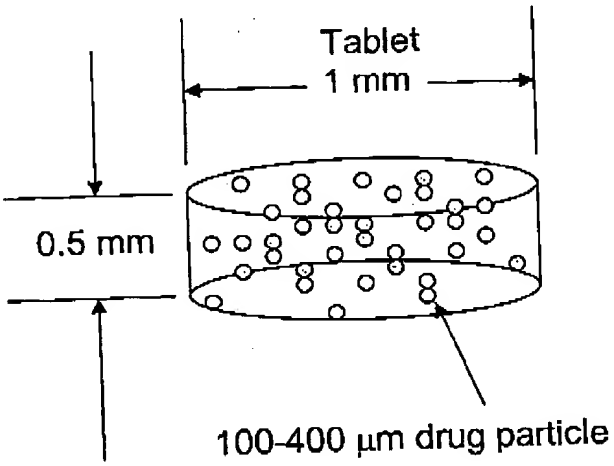
Green *et al.* teach a process for preparing rapidly disintegrating solid dosage forms containing drug particles, wherein the drug particles may be *coated or uncoated* with a water-insoluble polymer or lipid material, resulting in a dosage form that exhibits delayed release of the drug for a sufficient period of time to provide for controlled or *sustained release* of the drug after swallowing. The drug particles have a size such that the coatings can be formed thereon which are sufficiently *intact and continuous* to prevent or minimize loss of drug during processing. The coarse drug particles have an average particle size up to about 500 μm. In this size range, it is possible to apply a *uniform intact coating* on the particle in order to achieve efficient freeze-dried dosage forms with slow drug release rate (see reference cols. 1, line 5 – col. 3, line 22); (col. 5, lines 1-47).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the combined teachings of Moro *et al.* and Green *et al.* because Moro *et al.* teach an active ingredient formulation (i.e., glycyrrhizinate) whereby a core powder is coated and covered by a sheath powder and similarly Green *et al.* teach a dosage form comprising drug particles that are either coated or uncoated and if coated, provide a continuous intact coating on the drug particles in order to provide a sustained release of the active ingredient. The expected result would be a continuously coated, non-porous pharmaceutical formulation that exhibits a sustained release of the active drug material, as similarly desired by the Applicant(s).

Applicants respectfully disagree with the Examiner's above assertion that "expected result" of combining the teachings of Moro and Green would be a "continuously coated, non-porous pharmaceutical formulation *that exhibits sustained release of the active drug material*, as similarly desired by Applicant(s)".

First of all, Applicants note that when Green discloses "controlled or sustained release after swallowing", Green is referring to a "freeze-dried tablet dosage form

containing [a plurality of] drug particles which may be uncoated or coated with a polymer or lipid material". In other words, the disclosed "controlled or sustained release after swallowing" is provided by a large tablet comprising a continuous phase having a plurality of coated drug particles therein, such as depicted below.



See the first paragraph of Green's detailed description copied below:

It has now been found, in accordance with the present invention, that it is possible to produce fast dispersing dosage forms which disintegrate rapidly in the mouth and which do not depend on the use of sweetening or flavoring agents to mask the taste. The dosage forms have good mouth feel and do not exhibit premature release of the drug in the mouth. The invention is based on the discovery that it is possible to produce a fast dispersing freeze-dried dosage form containing drug particles which may be uncoated or coated with a polymer or lipid material which exhibit minimal release of the drug in the mouth. This is achieved by using coarse coated drug particles and controlling the viscosity of the suspension by reducing the temperature during the holding time in suspension to minimize sedimentation of the particles without altering the physical properties of the dried units. The resulting dosage form exhibits delayed release of the drug for a time at least sufficient to mask the taste in the mouth before swallowing, and typically for a longer period of time to provide controlled or sustained release of the drug after swallowing.

A full review of Green would be helpful to make it clear that there is no possible way that Green cannot make up for the admitted deficiencies of Moro, Sakon, and Haynes, because Green is not combinable with Moro, Sakon, and Haynes. Paragraph 15

of the Declaration provides sworn evidence that "Green's teaching relates to placing coated drug particles in suspension in a process to form a bulk dosage form (fast-dissolving tablet) incorporating a plurality of drug particles. This teaching would clearly be of no benefit to Moro, Sakon or Hayes".

Applicants again provide a detailed review of Green to ensure Green is understood for what it actually teaches, and what it does not teach. Green discloses a process for preparing an oral solid rapidly disintegrating freeze-dried bulk dosage form (tablet) of a pharmaceutically active substance having an unacceptable taste. Prior to freeze drying, a suspension of uncoated or coated coarse particles of a pharmaceutically active substance is disposed in a carrier material and is then cooled to reduce the viscosity and minimize release of the active substance during processing, as well as beyond the point of disintegration of the form in the mouth, to minimize bad taste from the drug. The continuous phase (e.g. water) is removed and the resulting final composition is generally 1 mm or greater in size discrete units containing up to 250 mg of the drug (col. 6 line 49), such as tablet shaped articles with small (uncoated or coated) drug particles dispersed throughout, analogous to a "plum pudding" of drug particles in a sea of freeze dried coating material (such as gelatin) as shown in the tablet image provided above. Example 2 of Green is copied below in its entirety:

Example 2

Material	%
Purified water	74.99
Gelatin	3.00
Mannitol	2.50
Coated paracetamol	19.51
FDC Blue No. 2	0.0025

The gelatin and mannitol were added to the water and heated to 40 C. to dissolve before allowing to cool to 23 C. The mix was gradually added to the coated paracetamol (200 µm particles, 82% potency, coated with a water insoluble polymer) with manual mixing until a fluid suspension was formed. The process was the same as in Example 1. Viscosity values obtained are quoted at a shear rate of 500 s^{-1}. 0.5 ml aliquots (80 mg paracetamol) of the suspension were also dosed manually using a Gilson pipetteman into preformed PVC/PVdC blisters which were then frozen rapidly at -80 C. Freeze drying was then performed using a standard cycle. The blisters were then sealed with foil.

The temperature of the mix was then adjusted, and after allowing to equilibrate for 45 minutes the measurements and dosing was repeated.

Temperature (.degree. C.)	Viscosity (mPa · s)	% sedimentation in 5 mines	Tensile Strength Nmm^{-2}	Disintegration time(s)
23.0	36.04	33	0.536	1.4
21.0	42.66	8.9	0.561	1.4
18.7	53.08	0	0.553	3.4
17.6	51.01	0	0.598	3.7
14.9	73.06	0	0.630	3.5

The results demonstrate the increase in viscosity of the suspension as the temperature is decreased. The disintegration times of the units do increase very slightly but are still rapid at viscosity levels sufficient to prevent any sedimentation in 5 minutes. When tasted, the units dispersed in the mouth with no bitter taste.

Thus, as noted in Applicants' Reply filed on July 8, 2004, the particle coating step, and the resulting coated drug particles, which is the focus of Applicants' claimed invention, is outside the scope of Green. Green does not provide any teaching regarding how to form discrete coated drug particles as claimed by Applicants. Green only uses coated (or uncoated) drug particles in his suspension process to form a bulk dosage form (fast-dissolving tablet) incorporating a plurality of coated drug particles, the *tablet* disclosed to provide the "controlled or sustained release after swallowing".

Green relies on "current coating techniques", such as to provide the paracetamol (200 µm particles, 82% potency) coated with a water insoluble polymer disclosed in

Example 2 above, and provides the following teaching regarding the same (col. 3, lines 9-21):

> Current coating techniques are able to effectively coat particles greater than 100 μm, whereas particles less than *100 μm may not have an intact coat*, which will result in rapid release of the drug once in suspension. Coating of larger particles therefore decreases the rate of release of drug. Typically, according to the present invention, the coarse particles may have a size of up to 1 millimeter, although the average size is generally up to about 500 μm, for example 75 to 400 μm, more usually in the region of about 100-300 μm. *In this size range, it is possible to apply a uniform intact coating on the particle in order to achieve efficient freeze-dried dosage forms with slow drug release rate*. (italics for emphasis only).

In addition, col. 5, lines 27-52 of Green discloses the following:

> Generally, the coating on the particles is a polymer or lipid material and serves to prevent loss of the pharmaceutical agent during processing, as well as delaying release of the pharmaceutically active substance beyond the point of disintegration of the form in the mouth. Any suitable polymer or lipid or combination can be used as the coating material. Examples of suitable polymers include cellulose and derivatives such as ethylcellulose, hydroxyethylcellulose, hydroxypropylmethylcellulose, hydroxypropylcellulose, methylcellulose, cellulose acetate, cellulose acetate phthalate, hydroxypropylmethylcellulosephthalate, acrylic derivatives, such as polymethacrylates, polyglycolic--polylactic acid, polyvinylalcohol, gelatin, collagen and polyethyleneglycol. Examples of suitable lipid materials include waxes such as beeswax and lanolin, stearic acid and derivatives such as glycerol esters, fixed oils, fats, phospholipids, and glycolipids.
>
> *Such coatings are well known to persons skilled in this art*. Persons skilled in the art could also readily provide coatings having a particular dissolution time so as to ensure that drug release is prevented until required. (italics for emphasis only)

Thus, Green does not cure the deficiencies of Moro, Sakon and Hanes as it is <u>not</u> combinable with the same. Significantly, as noted above, Green provides evidence that core particles obtained using known techniques (which although not explicitly disclosed would include the well known spray techniques disclosed in Moro, Sakon and Hanes references) must be at least 75 μm, more usually in the region of about 100-300 μm, to achieve a "uniform intact coating on the particle" to achieve "efficient freeze-dried

dosage forms with slow drug release rate". This minimum size information is consonant with the Maa paper and Jones patent of record submitted by the Applicants previously.

Paragraph 13 of the Declaration provides sworn testimony supporting this proposition:

The intermediate coated drug particles formed by the non-ascertainable "current coating techniques" are disclosed by Green as having to be at least 100 μm, or more (e.g. 500 μm) in size to permit the formation of a continuous coating thereon. Green's "current coating technique" relied on is likely the spray drying technique disclosed by Moro, Sakon and Hayes, but cannot be sure because of the absence of any specifics. Accordingly, the "current coating techniques" alluded to by Green provides no teaching that can be used to improve upon the spray dry coating results obtainable using the processes disclosed by Moro, Sakon or Hayes. Therefore, Green's intermediate coated particles and associated method are not combinable with the coated particles and associated spray-on method disclosed by Moro, Sakon or Hayes. As a result, the compositions provided by Moro, Sakon or Hayes cannot benefit from a knowledge of Green to achieve "a continuously coated, non-porous pharmaceutical formulation that exhibits a sustained release of the active drug material" as asserted by the Examiner.

Beginning on page 13 of the Final Office Action, in the section entitled "Response to Arguments," the Examiner asserts that:

> Firstly, Applicant argued, "Applicant's process of laser ablation permits formation of continuous nanoscale coatings on 50 μm (or less) core particles. Such coated particles are not disclosed by any of the references cited herein". Applicant also argued regarding the attached paper (Maa *et al.*) and US Pat. No. 5, 437.889 (Jones et al) to demonstrate "that when spray processing is used, the core particles must be at least about 75 to 100 μm or larger to obtain continuous coatings."
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> These arguments have been thoroughly considered, but were not found persuasive. Applicant has not established that less than 50 μm constitutes a critical maximum upper

limitation as to provide unexpected results over the prior art. Note that the specification permits the use of >50 μm which would include the range taught by Green ('577).

Secondly, Applicant argued, "Green does not cure the deficiencies of Moro, Sakon and Hanes. Green provides evidence that core particles obtained using known techniques must be at least 75 μm, more usually in the region of about 100-300 μm to achieve a uniform intact coating on the particle to achieve efficient freeze-dried dosage forms with slow drug release rate."

This argument has been considered but was not persuasive. Although Green *et al.* at column 3, lines 15-18, makes reference to, 'for example 75 to 400 μm', Green *et al.* also teaches that the particles generally have an average size of *up to about 500 μm*. The 'up to about 500 μm' would include particles having a particle size of <50 μm, as instantly claimed. Additionally, Green *et al.* claims, in claim 10, particles having a size in the range of 50 μm to 400 μm. Thus, Green *et al.* recognize the advantages obtained through the utilization of small particulate micron sizes.

Thirdly, Applicant argued, "The size of Applicant's claimed nanoscale thick (1 to 500 nm) coated drug particles (<50 μm in diameter) provide unique biological responses."

This argument has been considered but was not persuasive. The prior art clearly recognizes limitations of delivery based on micron size. The argument of the ability of smaller particles to be more successful in drug delivery via inhalation does not represent an unexpected result. The result is well known in the art. Moreover, one of ordinary skill familiar with this art would be fully capable of determining suitable or effective micron sizes, through the use of routine or manipulative experimentation to obtain the best possible results, dependent on the desired purpose.

Regarding the Examiner's assertion above that "Applicant has not established that 50 μm constitutes a critical maximum upper limitation as to provide unexpected result over the prior art, and that the [Applicants'] specification permits use of >50 μm which

would include the range taught by Green", Applicants first respectfully note that it is well established in the patent law that claims can, and almost always do, have a scope that is narrower than the scope of the invention described in the specification. Applicants also respectfully remind the Examiner that the invention relates to not only coated drug particles but also *methods* for preparing coated drug particles. The laser ablation method for coating drug particles is novel, even for larger >50 μm core particles. Accordingly, the specification permitting use of >50 μm core particles should not influence the patentability determination of smaller coated drug particles according to the invention.

As testified to in paragraph 6 of the Declaration, it is the combination of the claimed continuous nanoscale thickness (1 to 500 nm) on core drug particles (< 50 μm in diameter) which provide unique and unexpected biological responses. Paragraph 6 of the Declaration is copied below:

> The coated drug particles described in the '415 application includes particles which provide unexpected and/or new results by virtue of their size, including a change in function which permits new and highly advantageous applications. I do not dispute the Examiner's assertion that the "prior art recognizes limitations based on micron size particles", since it was known at the time of the invention that particles greater than about 20 to 50 μm in size are not inhalable by individuals. However, prior to the invention, continuously coated drug particles having sizes less than 50 μm in size were not obtainable.
>
> Specifically, the size of Applicants' claimed nanoscale thick (1 to 500 nm) coated drug particles (< 50 μm in diameter) provide unique and unexpected biological responses. Particles according to the invention provide rapid and complete dispersion, as well as sustained release, such as for several hours. Sustained release is demonstrated through a release profile showing an essentially linear release rate over the period of several minutes to several hours (see Example 1, page 33, lines 18-20; Example 2 (beginning on page 34, line 28) demonstrating an improved sustained release rate profile compared to the uncoated drug particles. A 90% release occurred at approximately 12 hours (for coating at 2 hertz) and beyond 24 hours (coating at 5 hertz), compared to uncoated drug particles that reached 90 % release at approximately 2 hours (see Figs. 6 and 7). Similarly, in Example 3 (page 36, lines 11-14), in vitro dissolution of coated rifampicin reached 90% release after 6 hours compared to 90% release after 15 minutes for the uncoated rifampicin (Fig. 8)).

Such sustained release profile obtained using continuously coated particles according to the invention were unexpected based on release data reported from somewhat thicker continuous coatings. The release profile for these thicker coatings are known to be characterized by a delayed release, rather than a sustained release, with no significant release throughout the first several hours. Sustained release for a drug is important in many applications. For example, regarding a painkiller, some early release (first few minutes) which is sustained for several hours keeps the concentration of the painkiller in the bloodstream above a therapeutic level for a long duration, such as 8-12 hours, rather than a burst release, whether with a delay or not, that is quickly (e.g. less than 1 hour of therapeutic use) carried away to the liver.

A hypothetical "micron-scale" continuously coated drug particle (>100 μm) is clearly too large to be used for inhalation (depositing in the mouth or throat) and release of the core drug over many hours to several days, and not generally obtainable by spray coating because the result from spray drying is inherently a continuous phase having a plurality of core particles therein, not the coated discrete drug particles which are claimed in the '415 Application.

Regarding Green's disclosure of core particles having a size up to about 500 μm, including <50 μm as instantly claimed, Green claiming particles from 50 μm to 400 μm, and Green recognizing the advantage of small particulate micron sizes, Applicants do not dispute that the advantages of small particles sizes are well known, and Green includes 50 μm core particles in his tablet comprising a plurality of coated particles. However, Green teaches that the 50 μm core particles will not be continuously coated. Applicants once again call attention to Green's specification, (col. 3, lines 9-21):

> Current coating techniques are able to effectively coat particles greater than 100 μm, whereas particles less than *100 μm may not have an intact coat*, which will result in rapid release of the drug once in suspension. Coating of larger particles therefore decreases the rate of release of drug. Typically, according to the present invention, the coarse particles may have a size of up to 1 millimeter, although the average size is generally up to about 500 μm, for example 75 to 400 μm, more usually in the region of about 100-300 μm. *In this size range, it is possible to apply a uniform intact coating on the particle in order to achieve efficient freeze-dried dosage forms with slow drug release rate.* (italics for emphasis only).

Accordingly, Green's disclosure of 50 μm core particles are not continuously coated as compared to the continuously coated drug particles claimed by Applicants. As testified to in paragraph 12 of the Declaration:

Green relies on "current coating techniques", such as to provide drug particles (e.g. paracetamol 200 μm) coated with a water insoluble polymer and notes that "Current coating techniques are able to effectively coat particles greater than 100 μm, whereas particles less than *100 μm may not have an intact coat*, which will result in rapid release of the drug once in suspension." (col. 3, lines 9-21). Therefore, although Green's teaching of particles generally having an average size up to 500 μm would mathematically include particle sizes less than 100 μm as asserted by the Examiner, particles having sizes less than 100 μm are not included by Green because they lack "an intact (continuous) coat".

Likely, the continuous phase of the tablet delays the release somewhat of non-continuously coated drug particles rendering the taste not too awful. Although it is indeed desirable to provide small continuously coated drug particles, Applicants are the first to provide the same in the claimed range.

The Examiners assertion "thirdly, the size of Applicant's claimed nanoscale thick (1 to 500 nm) coated drug particles (< 50 μm in diameter) provide unique biological response" not being persuasive has been largely addressed above. Although Applicant's claimed nanoscale thick (1 to 500 nm) coated drug particles (< 50 μm in diameter) are highly desirable based on the unique and unexpected biological response described above, the routine or manipulative experimentation suggested by the Examiner to obtain "the best possible results, dependent on the desired purpose" to achieve Applicants' claimed nanoscale thick (1 to 500 nm) coated drug particles (< 50 μm in diameter) cannot be used to obtain Applicants' claimed coated drug particles. Known spray-drying processes used by all the cited references cannot provide Applicants' claimed nanoscale thick (1 to 500 nm) coated drug particles (< 50 μm in diameter) made possible by the enabling laser ablation technology disclosed in the application. Paragraph 16 of the declaration provides sworn testimony that;

spray drying cannot form a plurality of coated particles as it instead forms *a porous continuous phase having a plurality of core particles therein. Moreover, spray*

drying clearly cannot provide a medicament comprising < 50 micron core drug particles coated with a nanoscale continuous and non-porous coating layer. Applicants' claim 28 which recites a plurality of coated drug particle having a diameter of less than 50 μm, the coating layer being a continuous and non-porous layer, having an average thickness of the between 1 and 500 nm is thus not obtainable in my opinion based on the cited art, whether alone or in combination.

Accordingly, claim 28, closely related method claim 66, and their respective dependent claims are patentable over the cited art.

Certain dependent claims provide independently patentable limitations. Most notably, claim 29 recites "wherein said coating layer is exclusive of said drug provided by said drug particles". Although claim 29 was rejected in the Final Office Action, NO BASIS FOR REJECTING CLAIM 29 WAS PROVIDED. The cited art which utilizes spray-drying cannot provide a coating layer free of the drug. As noted earlier, solution based methods, such as spray methods, invariably include some drug in the coating due to varying degrees of solubility of the drug in the solution. Laser ablation according to the invention is a dry process which provides a coating layer free of the drug.

Applicants have made every effort to present claims which distinguish over the cited art, and it is believed that all pending claims are in condition for allowance. However, Applicants request the Examiner to call the undersigned (direct dial 561-671-3662) after review of this Reply if the Examiner determines that any clarification is necessary to permit issuance of a Notice of Allowance.

Respectfully submitted,

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